IN THE CLAIMS

1-30. (Cancelled)

31. (Currently amended) A method for evaluating carcinogenicity of an agent, comprising the steps of:

contacting a test agent with a human cell;

determining the level of expression of at least one transcript or its translation product in the human cell after contacting with the agent; wherein the transcript is of a gene selected from a first group consisting of genes IG GAMMA-1 CHAIN C REGION (HUMAN), Human 1 g gamma3 heavy chain disease OMM protein mRNA, 274912 MYELIN TRANSCRIPTION FACTOR 1 (Homo sapiens), 152524 CYCLIN-DEPENDENT KINASE INHIBITOR 1 (Homo sapiens), H. sapiens mRNA for 43 kDa inositol polyphosphate 5-phosphatase, Human N-acetylgalactosamine 6-sulphatase (GALNS) gene, exon 14, 155730 KERATIN, TYPE I CYTOSKELETAL 17 (HUMAN), H. sapiens mRNA (clone 9112), kinase related protein, Human placental cDNA coding for 5'nucleotidase (EC3.1.3.5), H. sapiens MLN62 mRNA, Human activated p21cdc42Hs kinase (ack) mRNA, complete cds., 81780 COMPLEMENT C4 PRECURSOR (Homo sapiens), 172486 clone, mRNA for tuberin, or TSC2 gene, Homo sapiens ~~of~~ cardiac alpha-myosin heavy chain gene~~,~~, KERATIN, TYPE II CYTOSKELETAL 5 (HUMAN); contains MSR1 repetitive element, 182000 FK506-BINDING PROTEIN PRECURSOR ~~(Mus musculus)~~, Human insulin-like growth factor-binding protein-3 gene, complete Cds, clone HL1006d, 72466 ALPHA CRYSTALLIN B CHAIN (HUMAN), Homo sapiens mRNA for serum response factor-related protein, RSRFR2, 198656 HEPATOCYTE GROWTH FACTOR-LIKE PROTEIN PRECURSOR (Homo sapiens), 62461

SMALL ~~NCUELAR~~ NUCLEAR RIBONUCLEOPROTEIN ~~RIBONUCLEORPORTEIN~~ Particle N (SNRPN), contains MSR1 repetive element, 155335 INTEGRIN ALPHA-3 (Homo sapiens), 41792 TUBULIN BETA-2-CHAIN (HUMAN), Human estradiol 17 beta-dehydrogenase gene, complete cds, H. sapiens mRNA for cystathionine-beta-synthase, Homo sapiens of cardiac alpha-myosin heavy chain gene, Human mRNA for thyroglobulin, Human guanine nucleotide regulatory protein (ABR) mRNA, complete cds, Human novel growth factor receptor mRNA 3' Cds, 142899 DNA-DIRECTED RNA POLYMERASE III LARGEST SUBUNIT ~~(Plasmodium falciparum)~~, Human mRNA for collagen VI alpha-1 C-terminal globular domain, Homo sapiens sodium channel type I, beta subunit (SCN1B) mRNA, complete cds., 50887 GUANINE NUCLEOTIDE DISSOCIATION STIMULATOR RALGDSA ~~(Mus musculus)~~, Human cytochrome P450 4F2 (CYP4F2) mRNA, complete cds, Human MAGE-2 gene exons 1-4, complete cds, H. sapiens mRNA for transforming growth factor alpha, 38251 H sapiens HSJ1 mRNA, p53, H. sapiens mRNA for intestine-specific annexin, KERATIN, TYPE ICYTOSKELETAL 15 (HUMAN); contains MER20 repetitive element 5065 GROWTH ARREST AND DNA-DAMAGE-INDUCIBLE PROTEIN GADD45 (Homo sapiens), Human steroidogenic acute regulatory protein (StAR) mRNA, complete cds, LYSYL HYDROXYLASE (PLOD), (HUMAN); 151767 FASL RECEPTOR PRECURSOR (Homo sapiens), Homo sapiens creatine transporter mRNA, complete cds, KERATIN TYPE I CYTOSKELETAL 15 (HUMAN); contains MER20 repetitive element, Human mRNA for thyroperoxidase, 275040 HEPATOCYTE GROWTH FACTOR-LIKE PROTEIN PRECURSOR (HUMAN), 121731 CYTOCHROME P450 IVB1 ~~(Rattus norvegicus)~~, Homo sapiens dopamine transporter (SLC6A3) mRNA, complete cds, 139080 COMPLEMENT

DECAY-ACCELERATING FACTOR 1 PRECURSOR (Homo sapiens), H. sapiens mRNA for caveolin, Human endogenous retrovirus type C oncovirus sequence, 31481 TYROSINE-PROTEIN KINASE HCK (Homo sapiens), Homo sapiens ribosomal protein S6 kinase 2 (RPS6KA2) mRNA, complete cds, Human Fas antigen (fas) mRNA, complete cds, Human mRNA encoding pregastrin (a regulatory hormone of gastric acid secretin and growth of the gastrointestinal mucosa), H. sapiens mRNA for placental growth factor (PIGF), H. sapiens mRNA for placenta growth factor (PIGF), Human PML-2 mRNA, complete Cds, Human mRNA (KIAA0027) for ORF, partial cds, Human placenta-specific growth hormone mRNA, complete cds, Human high conductance inward rectifier potassium channel alpha subunit mRNA, complete cds, Human cytochrome P450 IID6 (CYP2D6) gene, complete cds, 180447 FIBROBLAST GROWTH FACTOR RECEPTOR 3 PRECURSOR (Homo sapiens), 153585 EBNA-2-NUCLEAR PROTEIN (Epstein-Barr virus), 36678 TROPONIN C, ISOFORM 2 ~~(Balanus nubilis)~~, 182125 HDL-BINDING PROTEIN, HUMMLC2At; Homo sapiens; 593 base pairs, 80486 LIVER CARBOXYLESTERASE PRECURSOR (HUMAN), 121916 NEUTRAL CALPONIN, SMOOTH MUSCLE ~~(Sus scrofa)~~, Human 11 beta-hydroxysteroid dehydrogenase type II mRNA, complete cds, Homo sapiens interferon regulatory factor 1 gene, complete cds, Human Fas antigen (fas) mRNA, complete cds, NEUTROPHIL OXIDASE FACTOR (p67 PHOX) (HUMAN), Human 11 kd protein mRNA, complete cds, Human semaphorin V mRNA, complete cds, MYELIN TRANSCRIPTION FACTOR 1 (HUMAN), 175991 NEURONAL CALCIUM SENSOR 1 ~~(Rattus norvegicus)~~, 81422 HUMAN SMOOTH MUSCLE ALPHA-ACTIN (AORTIC TYPE), Human mRNA for irp protein (int-1 related protein), Human Fas antigen (fas) mRNA, complete cds, Human beta-migrating plasminogen activator inhibitor 1

mRNA 3' end, 26063 COMPLEMENT C4 PRECURSOR (Homo sapiens), 142450 VASCULAR ENDOTHELIAL GROWTH FACTOR PRECURSOR ~~(Rattus norvegicus)~~, Human visinin-like peptide 1 homolog mRNA, complete cds, H. sapiens mRNA for red cell anion exchanger (EPB3, Ae1, Band 3) 3' non-coding region, Human laminin S B3 chain (LAMB3) mRNA, complete cds, Human cytochrome P450 IID6 (CYP2D6) gene, complete cds, Human hexokinase 1 (HK1) mRNA, complete cds, Human mRNA for the MDM2 gene, Human mRNA for cytochrome P-450LTBV, RYANODINE RECEPTOR, SKELETAL MUSCLE (HUMAN), 39052 POTASSIUM CHANNEL PROTEIN EAG ~~(Drosophila melanogaster)~~, and 124416 SERINE THREONINE-PROTEIN KINASE COT-1 ~~(Neurospora crassa)~~ ~~in Figure 1 and~~ or a second group consisting of genes ~~numbered 7-24, and 26-100~~ 196105 PLACENTAL CALCIUM-BINDING PROTEIN (HUMAN), 127228 HEAT SHOCK PROTEIN, CHAPERONIN 10, or GroES; MITOCHONDRIAL, H. sapiens Id1 mRNA, 51894 GTP-BINDING NUCLEAR PROTEIN RAN (Homo sapiens), 84680 ATP SYNTHASE ALPHA CHAIN, MITOCHONDRIAL PRECURSOR (HUMAN), Human non-histone chromosomal protein HMG-17 mRNA, complete cds, PHOSPHOGLYCERATE MUTASE, BRAIN FORM (HUMAN), Human mRNA (KIAAO108) or ORF (complete cds) and HepG2 mRNA identical sequence, 115413 HEAT SHOCK PROTEIN HSP 84 ~~(Mus musculus)~~, 78161 PROFILIN I (HUMAN), ~~124693 RAT mRNA for PROTEASOME SUBUNIT RC10-11, or~~ HUMAN PROTEASOME SUBUNIT HSC10-11, 131036 TRANSFERRIN RECEPTOR PROTEIN (Homo sapiens), 214923 PSORIASIS-ASSOCIATED FATTY ACID BINDING PROTEIN HOMOLOG (HUMAN), Human mRNA (KIAA0098) for ORF (human counterpart of mouse chaperonin containing TCP-1 gene), partial cds, Human mRNA for ORF(KIAA0101), complete

cds, 274422 ATPASE INHIBITOR, MITOCHONDRIAL ~~(BOVIN)~~, Human hnRNP A2 protein mRNA, 46019 MCM3 HOMOLOG (HUMAN), Human Ku autoimmune antigen gene, complete cds; Homo sapiens pst1 mRNA for pancreatic secretory inhibitor (expressed in neoplastic tissue), Human esterase D mRNA 3'end, 49970 LUPUS LA PROTEIN (HUMAN), H. sapiens mRNA for TRAP beta subunit, 125446 TRANSCRIPTION INITIATION FACTOR TFIID (Homo sapiens), Human mRNA for human homologue of rat phosphatidylethanolamine binding protein, complete cds, 120041 HLA-DR ASSOC. PROTEIN I, P31 (also called Ii, In, M1, Dr gamma, XM 1) (Homo sapiens), Human protein-tyrosine phosphatase (HU-PP-1) mRNA, partial sequence, Homo sapiens integral nuclear envelope inner membrane protein (LBR) gene, complete cds, 52626 HYPOTHETICAL GTP-BINDING PROTEIN IN PMI40-PAC2 INTERGENIC REGION ~~(Saccharomyces cervisiae)~~, H. sapiens mRNA for ATP-citrate lyase, Human mRNA for ORF (KIAA0102), complete cds, 238612 Human bumetanide-sensitive NA-K-Cl cotransporter (NKCC1 or BSC2) mRNA, complete cds, 26573 STATHMIN (Homo sapiens), H. sapiens mRNA for DNA primase (subunit p48), Human c-myb mRNA, 3'end, Human superoxide dismutase (SOD3 or EC-SOD) gene, complete cds, Human mRNA encoding IMP:pyrophosphate phosphoribosyltransferase E.C. 2.4.2.8, Human synexin mRNA, complete cds, Human p62 mRNA, complete cds, Human mRNA for mitochondrial 3-oxoacyl-CoA thiolase, complete cds, Human mRNA (K1AA0094) for ORF (yeast methionine aminopeptidase-related), partial cds, 204299 REPLICATION PROTEIN A 14 KD SUBUNIT (HUMAN), H. sapiens mRNA for translin, 117708 MYOSIN HEAVY CHAIN, CLONE 203 ~~(Hydra attenuata)~~, Human mRNA (KIAA0088) for ORF (alpha-glucosidase-related), partial cds, Human mRNA (KIAA0035) for ORF (rat 140 kd nucleolar phosphoprotein homologue),

partial cds, Human effector cell protease receptor-1 (EPR-1) gene, partial cds, 112020 C-1-TETRAHYDROFOLATE SYNTHASE, CYTOPLASMIC (HUMAN), 40874 TUBULIN GAMMA CHAIN (HUMAN), 42829 EUKARYOTIC INITATION FACTOR 4B (Homo sapiens), PROFILIN II (HUMAN), 40753 RAN-SPECIFIC GTPASE-ACTIVATING PROTEIN, ranGAP (Homo sapiens), Human mRNA for ORF (KIAK0002), or HUMAN D-TYPE CYCLIN complete cds, 128385 HAMSTER RNA FOR CYCLIN B2 ~~(Mesocricetus auratus)~~, PYRROLINE-5-CARBOXYLATE REDUCTASE (HUMAN), 150169 EUKARYOTIC INITIATION FACTOR 4E (Homo sapiens), 72050 NUCLEOTIDE-SENSITIVE CHLORIDE CHANNEL ~~(Canis familaris)~~, or HUMAN CHLORIDE CHANNEL REGULATORY PROTEIN mRNA, Homo sapiens CD24 signal transducer mRNA, complete cds and 3'region, H. sapiens mRNA for cathepsin C (dipeptidyl peptidase 1), Homo sapiens monocarboxylate transporter 1 (SLC161A1) mRNA, complete cds, 68690 U1 SMALL NUCLEAR RIBONUCLEOPROTEIN A (HUMAN), Human serine kinase (SRPK1) mRNA, complete cds, 209484 CD9 ANTIGEN (Bos taurus), or HUMAN T245 PROTEIN, Human glutamate dehydrogenase (GDH) mRNA, complete cds, 109334 NEGATIVE REGULATOR OF MITOSIS ~~(Emericella nidulans)~~, ~~77138 EUKARYOTIC INITIATION FACTOR 1A (Sac cerevisiae), or~~ HUMAN PROTEIN SYNTHESIS FACTOR 4C(elF-4C), H. sapiens mRNA for neuromedin U, Human chondroitin/dermatan sulfate proteoglycan (PG40) core protein mRNA, complete cds, H. sapiens mRNA for 2'-5' oligoadenylate binding protein, Human mRNA (KIAA0024) for ORF (putative human counterpart of Chinese hamster phosphatidylserine synthase gene), complete cds, Human MAC30 mRNA, 3'end, 74167 APOLIPOPROTEIN A-11 PRECURSOR (HUMAN), 36504 GTPASE ACTIVATING PROTEIN ROTUND ~~(Drosophila~~

~~melanogaster)~~, 166353 CLEAVAGE STIMULATION FACTOR, 50 KD SUBUNIT (Homo sapiens), 127707 LAMININ BETA-1 CHAIN PRECURSOR (HUMAN), Human mRNA (K1AA0097) for ORF (novel protein), complete cds, 149556 O-antigen polymerase ~~(Shigella flexneri)~~, Homo sapiens E2F-related transcription factor (DP-1) mRNA, complete cds, NADH-UBIQUINONE DEHYDROGENASE 24 KD SUBUNIT PRECURSOR (HUMAN), Human methylmalonyl CoA mutase (MUT) gene, exon 13, 37866 BASIGIN PRECURSOR ~~(Gallus gallus)~~, 84443 GA BINDING PROTEIN BETA-1 CHAIN (Homo sapiens), Human erythroblastosis virus oncogene homolog 2 (ets-2) mRNA, complete cds, 53193 26S PROTEASE REGULATORY SUBUNIT 6 (Homo sapiens), S-ADENOSYLMETHIONINE DECARBOXYLASE PROENZYME (HUMAN), 26573 STATHMIN (Homo sapiens), 46827 VAV ONCOGENE (Homo sapiens), Human mRNA (KIAA0074) for ORF (yeast C728 protein-related), partial cds, Human DNA topoisomerase II gene (top2), gene 1, Homo sapiens cDNA clone 253186 3', 151010 EUKARYOTIC PEPTIDE CHAIN RELASE FACTOR SUBUNIT 1 (Homo sapiens), Human medium-chain acyl-CoA dehydrogenase (ACADM) mRNA, complete cds, and 121357 A49436 CDI1=CYCLIN-DEPENDENT KINASE INTERACTOR 1, wherein an agent which decreases the level of expression of a gene in the first group, or an agent which increases the level of expression of a gene in the second group is a potential carcinogen.

32. (Currently amended) The method of claim 31_wherein determining the level of expression of at least two of the transcripts or translation products is performed.

33. (Currently amended) The method of claim 31_wherein determining the level of expression of at least five of the transcripts or translation products is performed.

34. (Currently amended) The method of claim 31_wherein determining the level of expression of at least ten of the transcripts or translation products is performed.

35. (Currently amended) The method of claim 31_wherein determining the level of expression of at least twenty of the transcripts or translation products is performed.

36. (Currently amended) The method of claim 31_wherein determining the level of expression of at least fifty of the transcripts or translation products is performed.

37. (Currently amended) The method of claim 31_~~wheaein~~ wherein determining the level of expression of 70 of the transcripts or translation products is performed.

38. (Currently amended) The method of claim 31_wherein determining the level of expression of 90 of the transcripts or translation products is performed.

39. (Currently amended) The method of claim 31_wherein determining the level of expression of 100 of the transcripts or translation products is performed.

40. (Currently amended) The method of claim 31_wherein determining the level of expression of 125 of the transcripts or translation products is performed.

41. (Currently amended) The method of claim 31_wherein determining the level of expression of 145 of the transcripts or translation products is performed.

42-66. (Cancelled)

IN THE SPECIFICATION

At pages 4-5, substitute the following paragraph which spans the two pages:

Figure 1 is a Table showing genes induced by p53. The column headings are as follows. "Eb1" denotes the cell line EB1-ÿ , *i.e.,* a cell line which contains a zinc-inducible p53 gene. "EB" denotes the cell line EB1, a cell line which has a p53 mutant gene that fails to produce or express detectable p53 protein. "PM" denotes the number of perfect match oligonucleotides for a gene which hybridized and "MM" denotes the number of mismatch oligonucleotides for a gene which hybridized. "Ratio" is the ratio of intensity of EB1-ÿ to EB1. "Accession number" refers to a GenBank accession number. "EST?" if checked indicates that the function of the nucleic acid sequence has not been determined. "SAGE?" if checked indicates that analysis using the SAGE technique also detected this gene as p53-regulated. See ~~http://welchlink.welch.jhu.edu/~molgen-g/P53-SAGE.HTM~~ the website having a URL address of http file type, a domain name of welchlink.welch.jhu.edu, and the directory ~molgen-g/P53-SAGE.HTM.

At pages 6-7, substitute the following paragraph which spans two pages:

High density arrays are particularly useful for monitoring the expression control at the transcriptional, RNA processing and degradation level. The fabrication and application of high density arrays in gene expression monitoring have been disclosed previously in, for example, WO 97/10365, WO 92/10588, U.S. Application Ser. No. 08/772,376 filed December 23, 1996, now U.S. Patent No. 6,309,822; serial number 08/529,115 filed on September 15, 1995, now U.S. Patent No. 6,040,138; serial number 08/168,904 filed December 15, 1993 , now abandoned; serial number 07/624,114 filed on December 6, 1990, now abandoned; serial number 07/362,901

filed June 7, 1990, now abandoned, ~~all incorporated herein for all purposed by reference~~. In some embodiments using high density arrays, high density oligonucleotide arrays are synthesized using methods such as the Very Large Scale Immobilized Polymer Synthesis (VLSIPS) disclosed in U.S. Pat. No. 5,445,934 incorporated herein for all purposes by reference. Each oligonucleotide occupies a known location on a substrate. A nucleic acid target sample is hybridized with a high density array of oligonucleotides and then the amount of target nucleic acids hybridized to each probe in the array is quantified. One preferred quantifying method is to use confocal microscope and fluorescent labels. The GeneChip® system (Affymetrix, Santa Clara, CA) is particularly suitable for quantifying the hybridization; however, it will be apparent to those of skill in the art that any similar systems or other effectively equivalent detection methods can also be used.

REMARKS

The Amendments

The claims are amended to address formal matters and issues raised or noticed only in or after the final office action. They do not raise new issues and put the claims in better condition for appeal or allowance.

Oath/Declaration

The Patent and Trademark Office urges that the pending claims no longer substantially embrace the invention as set forth in the statement of the invention and/or in the original claims. Applicants respectfully traverse. The amendment merely substituted gene descriptions from Figures 1 and 2 for references to the same genes in Figures 1 and 2. Thus, only form but not content has changed. In view of this purely formal amendment, the pending claims embrace substantially the same invention as that originally filed.

No substitute declaration should be required under these circumstances.

Specification

1. Improper incorporation by reference is alleged but not explained. Applicants assume this relates to references at page 6, lines 20-27. Applicants have amended the specification to identify current status and have removed the incorporation by reference.

2. The embedded hyperlink has been removed from page 5.

35 U.S.C. §112, first paragraph

Claims 31-41 are allegedly not enabled by the specification.

One issue raised by the examiner is the animal species of some of the genes recited in the claims. The gene descriptions were imported into the claims from Figs. 1 and 2. Each gene is

represented by an accession number from Genbank. Each of the accession numbers relates to a human cDNA clone. See Exhibit I. Thus, each of the recited genes is a human gene. The reference to other non-human species have been deleted to clarify that human genes are intended.

The meaning of "homo sapiens of cardiac alpha-mysin" has been clarified by amending to recite "homo sapiens cardiac alpha-myosin."

The term "gene" in the claims is construed broadly by the Patent and Trademark Office to include both regulatory sequences and introns. Yet, the Patent and Trademark Office points out, some of the gene descriptions are of cDNAs. Because the claimed method is directed to assaying transcripts or translation products, and because transcripts and translation products do not have regulatory sequences or introns or features derived from them, this concern should be moot. Transcripts and translation products can be detected and their levels determined using the information provided in the specification. Complete gene sequences are not required to create nucleotide probes or antibodies to particular gene products. Thus, the claim's identification of genes using a coding sequence or even a partial coding sequence does not cause the claims to be not enabled.

Finally, the Office Action asserts that the claims are not enabled. The Office Action hypothesizes a comparison of two cell samples that are not in the same physiological state: one cell sample is nutritionally starved and one is amply fed.[1] Those of ordinary skill in the art know that cell based assays must be performed on cell samples that are physiologically similar. If cell samples are not physiologically similar, then there will be many differences between the cell samples that are not related to the agent one is testing.

1 The Office Action proposes feeding one sample with a culture medium called RPMI-1640 and depriving a control sample of culture medium.

If one were to compare fed cells to starved cells, one would likely obtain results that were not meaningful for carcinogenesis. Those of ordinary skill in the art would not, however, compare two cell samples that differed so grossly.

To properly assess the carcinogenicity of RPMI-1640, one of skill in the art might better design the experiment as follows:

1. Grow cells in a medium other than RPMI-1640.
2. Contact one half the cell sample with RPMI-1640 for a fixed period of time.
3. Wash the cells to remove RPMI-1640.
4. Grow both half cell samples in the other medium.
5. Test expression pattern.

Such a design would test two cell samples in the same physiological state. One of skill in the art is readily able to design such tests. One of skill in the art would not test RPMI-1640 by feeding one sample and starving the control sample.

The enablement issues raised have been addressed either by amendment or explanation. It is respectfully submitted that the claims are enabled and that the claims are in condition for allowance.

Respectfully submitted,

Dated: October 10, 2003

By: Sarah A Kagan
Sarah A. Kagan
Registration No. 32,141

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